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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Akzo Nobel N.V.
Velperweg 76
6824 BM Arnhem
PAYS-BAS

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Polytartrate composition

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Polytartrate composition

The present invention is concerned with a polytartrate composition for pulsatile release of a pharmaceutically active material, a process for preparing such a composition and the use thereof.

The modern medicinal therapy and prophylactics requires novel administration forms, which combine a controlled release rate of the pharmaceutically active material with high biocompatibility of the formulation. Different pharmaceutically active materials used in treatment of humans and animals require different release profiles. Pulsatile drug delivery is useful, for example, for the delivery of pharmaceutically active materials, that have short half-lives, and must be administered two or three times daily or with pharmaceutically active materials that are extensively metabolised pre-systemically or with pharmaceutically active materials, which loses the desired therapeutic effect when constant blood levels are maintained. It has long been appreciated that the release of certain pharmaceutically active materials in bursts or pulses at predetermined times following a single administration could have significant practical advantages in clinical or veterinary practice.

For example, an area of great interest for this type of delivery system is single-shot immunisation. In a classic immunisation regime, a single dose of a vaccine is delivered in one injectable or oral dose "primer" that is repeated one ore more times with "booster" doses for a long lasting immunity. Such multiple administration may not be practically feasible, especially for big numbers of livestock animals, e.g. chicken, pigs or cattle. A single-shot immunisation would deliver a second burst of antigen at a predetermined interval following a first burst, whereas the second burst would elicit a secondary immune response without the need for a second booster vaccination (repeat application).

Controlled-delivery-systems,-which-are-capable-of-pulsatile-release-could-be also useful for the delivery of hormones, especially for gonadotropins and growth hormones, because these hormones fail to produce their effects unless they are released intermittently. A potential use is in the field of livestock reproduction management, were e.g. follicle stimulating hormone (FSH) is currently applied to induce superovulation in cows.

A variety of compositions have already been developed to provide pulsatile release of various pharmaceutically active materials after oral and parenteral administration as described in e.g. the International patent application WO 92/17165, WO 93/17662, WO 93/03159, WO 96/12466, in US Patent No. 5,260,069, No. 5,656,298 or 5,429,822. Materials, which have been proposed for such controlled release systems, are biodegradable polymers, particular polyesters that are derived from hydroxycarboxylic acids. Much prior art has been directed to polymers derived from alpha-hydroxycarboxylic acid, especially to lactic acid in both its racemic and optically active forms (PLA), to glycolic acid (PGA) and to copolymers (PLGA) thereof such as e.g. described in US Patent No. 3,773,919.

In particular, it is known that, for many pharmaceutically active materials such compositions for providing time controlled pulsatile release may be obtained by using a barrier technology that is placed around the active ingredient, that is designed to degrade or dissolve after a certain time interval. One approach is the encapsulation the pharmaceutically active material in a suitable polymer, or by dispersing the pharmaceutically active materials in a matrix with one or more coatings to delay the release and determine the timing of the release.

Various complicated barrier structures are proposed, employing separate coating steps or the use of membrane reservoir devices for a pulsatile release of the pharmaceutically active material from the device. These barrier systems require additional steps in the manufacturing process and therefore increase the costs of such a device and make the manufacturing process very

complex. The manufacturing process should, however, preferably be simple, versatile and amenable to mechanisation and automatisation.

Another disadvantage of membrane reservoir compositions is the fact that the core active material can be released by dumping whenever the release-rate limiting membrane is ruptured. This could then result in the release of an undesired high, or even toxic, amount of the pharmaceutically active material.

Another disadvantage is, that during the manufacturing process organic solvents are used that should be better avoided, especially in parenteral compositions, because of the risk of local irritation after administration caused by solvent residues.

It was therefore desirable to find a composition for pulsatile release of pharmaceutically active material that is easy, robust and cost effective to manufacture and does not require a complex barrier system.

In US Patent application No. 5,391,696 depot preparations of polycondensates, which contain tartaric acid derivatives are described, that showed a uniformly controllable active substance release with a strongly decreased "initial burst" when they are used for depot preparations of pharmaceuticals. Such depot preparations, such as e.g. microparticles, that are manufactured by spray drying, and rod-shaped implants, that are manufactured by extrusion are described. Such a depot preparation is a dosage form that provides a profile in which the drug is released over a prolonged interval, at a substantially steady rate of release per unit of time.

Surprisingly the current inventors found that a polytartrate composition that is produced by simple compression releases the pharmaceutically active material in a pulsatile manner without the need of an additional barrier structure. Pulsatile release implies an initial first release followed by an almost release -free interval, after which a second dose of the pharmaceutically active material is released.

It was furthermore found, that such compositions, that overcome the drawbacks of prior art can be prepared using easy, robust and cost effective standard techniques that do not employ any solvents or heat and therefore do not lead to potential irritant solvent residues in the device.

Therefore the present invention provides a pharmaceutical composition comprising a polytartrate polymer and at least one pharmaceutically active material characterised in that the composition is in the form of a compressed tablet.

The composition according to the present invention can be in general a solid composition in various forms that is suitable for the release in an aqueous environment. Solid means solid at 25°C.

In Gennaro, Remington: The Science and Practice of Pharmacy" (20. Edition, 2000) Chapter 45, tablets are defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents that are prepared by either compression or compression moulding methods. Compressed tablets are manufactured by compression methods. These tablets are formed by compression and normally do not contain a special coating. They are made from powdered, crystalline, amorphous or granular materials, alone or in combination with binders, disintegrants, controlled release polymers, lubricants, diluents and in many cases colorants. The term "tablets" is used in herein encompasses solid pharmaceutical dosage forms for oral and parenteral administration to an animal or human body as well as for providing a topical formulation.

The polyesters to be used in the current invention are polytartrates, biodegradable polycondensates, which contain tartaric acid derivatives. Such polytartrates are described in US Patent No. 5,391,696 incorporated herein by reference. The term tartaric acid (dihydrosuccinic acid) as used in the present invention includes the two entantiomers (+)-tartaric and (-)-tartaric

acid and the racemate and the optically inactive mesotartaric acid and mixtures thereof. Polytartrates with a molecular weight of at least 15000 g/mol may be useful in the current invention.

Especially preferred are polycondensates which contain 2,3-O-alkylidenetartaric acid derivatives, 2,3-O-alkylidene-L-threitol, furo (2,5) groups or terephtalates, e.g. 2',3'-(1',4'-diethyl)-L-tartryl poly-(2,3-O-isopropylidene)-L-tartrate, 2',3'-O-isopropylidene-L-threityl poly-(2,3-O-isopropylidene)-L-tartrate, 2',3'-(1',4'-diethyl)-L-tartryl polyfurandicarboxylate, poly-(2,3-(1,4-diethyl)-L-tartyl) terephthalate, polylysine methylester 2,3-O-isopropylidene-L-tartamide.

Preferably 2'3'-(1',4'-diethyl)-L-tartryl poly-(2,3-O-isopropylidene)-L-tartrate is used.

The benefit of biodegradable polymers is that a surgical removal of the device after parenteral administration is unnecessary. Biodegradable means that the components are degraded into toxicologically harmless components in the course of time under physiological conditions, which are either metabolised or excreted by the human or animal body. The predetermined time delay (delay time prior to second release of the pharmaceutically active material) is in general dependent upon the rate of degradation of the materials, the water absorption by the device and the dissolution of the degradation products.

A polymer can be amongst other features characterised by its glass transition temperature. The polytartrate polymer, to be used in the current invention has a glass transition temperature that is greater than 40°C, preferably between 40°C and 60°C. The glass transition temperature (T_g) separates rubbery from glassy form behavior i.e. is that temperature at which an adhesive loses its flexibility and becomes hard, inflexible, brittle and "glasslike." If flexibility is required the glass transition temperature can be lowered e.g. by means of plasticizers.

The pharmaceutically active material to be used in the current invention can be generally a recombinant pharmaceutical or veterinary agent that has prophylactic activity (i.e. preventing diseases or pathological symptoms) or that has an activity for treating or curing pathological symptoms/ diseases in humans or animals (e.g. antiinflammatories). The pharmaceutically active material with prophylactic activity can be either a chemical (e.g. vitamins, minerals) or can be a biological e.g. antigen/antibody that e.g. triggers a protective immune response. The pharmaceutically active material to be used in the current invention is selected from one or more of antigens, antibodies or pharmaceutical substances. The pharmaceutically active material may comprise any native, synthetic or recombinant pharmaceutical or veterinary agent, or feed additive or supplement, including antigens, antibodies, antitoxins, nucleic acids, vaccines, cytokines, growth promoters, hormones, cancer cell inhibitory agents, immune stimulants or supressants, hypnotics, sedatives, tranquilisers, anti-asthmatics, antitussives, diuretics, anti-ulcer agents, anti-inflammatories, antiinfectives, anti-fungals, anti-viral agents, antiparasitics, vitamins, tonics, cardiovascular drugs, analgesics, stimulants, enzymes or minerals.

The pharmaceutically active ingredient may comprise one type of pharmaceutically active material or may be a mixture of different pharmaceutically active materials. The process of the present invention is especially advantageous for the incorporation of heat sensitive pharmaceutically active material, as no heat stress is employed during the manufacturing process of the device according to the invention. By heat sensitive pharmaceutically active material such material is meant that loses its activity and/or degrades at temperatures above the glass transition temperature of the polytartrate polymer. Furthermore no organic solvents are employed during the manufacturing process that allows the use of pharmaceutically active material that is sensitive to organic solvents.

The composition of the present invention may also be combined with another dosage forms which will combine the release profile of the novel composition with that of the other dosage form.

The amount of pharmaceutically active material used in the composition will vary from subject to subject, depending on age, general condition of the animal or human, the severity of the condition being treated and the type of the pharmaceutically active material. In general, an effective amount of pharmaceutically active material is employed meaning a non-toxic but sufficient amount to provide the desired therapeutic effect. Thus, it is not possible to specify an exact "effective amount". However, an appropriate "effective" amount in any individual case may be determined by a person skilled in the art using routine experimentation.

The composition according to the invention may optionally additionally comprise one or more of pharmaceutical acceptable excipients or adjuvants.

The term adjuvant is intended to include any substance, which is incorporated into or administered simultaneously with the immunogen, which potentiates the immune response in the subject. Adjuvants include but are not limited to mineral adjuvants e.g. aluminium hydroxide and aluminium phosphate or calcium phosphate, emulsions e.g. Freud's complete or incomplete adjuvant, microbial products e.g. BCG (attenuated Mycobacterium tuberculosis), lectins, saponins, immunostimulating complexes or liposomes.

The pharmaceutical or veterinary excipients may be e.g. used to influence the hydrophilic or lipophilic properties of the composition. The composition according to the current invention may further comprise pharmaceutical excipients known in the art e.g. as described in "Gennaro, Remington: The Science and Practice of Pharmacy" (20. Edition, 2000), incorporated by reference herein. Such pharmaceutical excipients are e.g. binders (e.g. gum tragacanth, PVP, cornstarch), disintegrating agents (e.g. corn starch, potato starch), diluents (e.g. lactose) and/or lubricants (e.g. magnesium stearate).

All such components, carriers and excipients must be substantially pharmaceutically or veterinary pure and non-toxic in the amounts employed and must be biocompatible and compatible with the pharmaceutically active material. Biocompatible in the present specification means that all components of the composition should be physiologically tolerable and should not cause an adverse histological response.

For preparation of the pharmaceutical composition according to the invention an effective amount of the pharmaceutically active material is mixed with the polytartrate polymer.

This mixture is than shaped by compression e.g. by direct compression, or compression moulding e.g. in a single punch press to form tablets of the desired size and shape, that are capable of being administered to a human or animal. After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and uniformity, which also are influenced both by the method of preparation and by the added tabletting excipients present in the composition.

The manufacturing process is performed at a temperature below the glass transition temperature of the polymer, preferably at room temperature and is characterised in that it includes the steps of:

a) mixing an effective amount of a pharmaceutically active material with the polytartrate polymer,

b) shaping the mixture by tabletting equipment to form compressed tablets.

A preferred method for forming the composition herein is by direct compression of a powdered mixture, alone or in combination with other excipients. Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself.

In more detail in a first step an effective amount of a pharmaceutically active material and the polytartrate polymer are mixed in a mixing equipment known in the art. The mixture is than sieved, to separate oversized particles and agglomerates. In a second mixing step optionally additional tabletting excipients are added as e.g. a lubricant (magnesium stearate) and/or colloidal silica (Aerosil) for improving the flow characteristics in order to reach a suitable mixture for the compression step. Optionally a second sieving step separates oversized particles. The mixture is than transferred to a tabletting equipment, e.g. a single punch press or a rotary tablet machine known in the art.

The tablet is formed by the pressure exerted on the mixture by the punches within the die. The compression force applied to the tablet is in the range between 15 and 65 kN/cm^2, preferably between 25 and 50 kN/cm^2.

The tablet assumes the size and shape of the punches and die used. The particular physical form of the tablets may vary according to the situation in which the system is used. The composition for administration directly to a human or animal body may be in any suitable shape including elongate, oval, round, capsule-form, square, triangular or cylindrical shape. Preferably the composition is cylindrical in shape for implants, as to produce devices which are adapted for implantation using a conventional device.

The composition of the current invention may be placed in the body of an animal or human which is desired to treat by any suitable known in the art technique, for example parenterally by subcutaneous or intramuscular injection, or by surgical implantation using conventional clinical or veterinary techniques, by administration into body cavities, by transdermal route or orally.

Alternatively the composition may be placed in an aqueous environment of animals, e.g. in a fish or shrimp pond to release pharmaceutically active materials for administration to aquatic animals (e.g. bath application).

In one preferred embodiment the composition according to the invention is implanted subcutaneously into a human or animal body. Implants are solid devices suitable for parenteral delivery and may be in a range of sizes for example from less than 1mm diameter to several cm depending on the species.

In another embodiment, the composition according to the invention may also be administered orally. Where the composition of the current invention is to be administered by oral ingestion, particularly to ruminants, it may be incorporated into a weighed capsule or bolus or other intra-ruminal device.

The recipient of the composition may be a human, a livestock animal e.g. sheep, cattle, pig, goat, poultry, a laboratory test animal, e.g. a rabbit, guinea pig, rat or mouse or a companion animal e.g. dog, cat or horse, a fish, shrimp or another aquatic animals or a wild animal.

Brief description of the figures:

Figure 1: In vitro release from PTA tablets containing 10 % Buserelin

Figure 2: The release from PTA tablets containing 10% and 5% Buserelin-acetate in a tablet of 3 mm diameter as a function of time.

Example

Preparation of (2'3'-(1',4-diethyl)-L-tartryl poly - (2,3 – o -isopropylidene) – L - tartrate (PTA) Buserelin - tablets

Table 1:

Tablet	PTA	Buserelin- acetate
Buserelin 10% – PTA tablet 5 mm	244,4 mg	28,6 mg
Buserelin 10% – PTA tablet 3 mm	126,2 mg	14,8 mg
Buserelin 5% – PTA tablet 3 mm	137,0 mg	7,3 mg

Buserelin (INN) is a synthetic nonapeptide and an analogue to the hypothalamus hormone gonadotropin. The amounts of 2'3'-(1',4'-diethyl)-L-tartryl poly-(2,3-o-isopropylidene)-L-tartrate (PTA) and of Buserelin-acetate as shown in table 1 were triturated in an agate mortar to obtain a homogeneous mixture. Subsequently, the mixture was compressed in a single punch press using flat-faced punches of 3 mm at a compression force of 48 kN/cm_2 or 5 mm in diameter at a compression force of 48 kN/cm^2 of 27 kN/cm^2 . The resulting tablets had a weight of 14 or 40 mg respectively. The size of the tablets has been determined with a calibrate vernier calipier.

In vitro release of Buserelin from the PTA tablets

Material and Methods: The tablets were prepared as described above. The weighted tablets were immersed in 12 ml phosphate buffer (0.05M, pH 7.4) containing 0.05% benzalconiumchloride and 0.1% sodium azide (release medium) and were incubated at 37°C for 4 weeks. At defined time points 8 ml of the release medium were withdrawn and replaced by fresh medium. Samples were analysed for Buserelin content by HPLC, using reverse phase HPLC with UV detection at 220 nm.

Results: Figure 1 shows the release from PTA tablets of 3 mm and 5 mm diameter containing 10% Buserelin- acetate as a function of time.

When the tablets were incubated in the release medium at 37°C, after an initial burst, the release drops to very small amounts from day 3 to day 10. During the first 10 days neither a mass loss, nor water absorption were observed. After 10 days water absorption and mass loss commence. In parallel, a remarkable increase in drug release ("*secondary burst*") occurs which continues over 2 - 4 days followed by a rather constant release up to the end of the release.

The release from PTA tablets containing 10% and 5% Buserelin- acetate in a tablet of 3 mm diameter as a function of time is shown in figure 2.

Claims

1. A pharmaceutical composition comprising a polytartrate polymer and at least one pharmaceutically active material characterised in that the composition is in the form of a compressed tablet.

2. The composition according to claim 1 characterised in that the polytartrate polymer is selected from the group of polycondensates which contain 2,3-O-alkylidenetartaric acid derivatives, 2,3-O-alkylidene-L-threitol, furo (2,5) groups and terephtalates.

3. The composition according to claim 2 characterised in that the polytartrate polymer is 2'3'-(1',4'-diethyl)-L-tartryl poly-(2,3-O-isopropylidene)-L-tartrate.

4. The composition according to any of the claims 1 to 3 characterised in that the polytartrate polymer has a glass transition temperature that is greater than 40°C.

5. The composition according to any of the claims 1 to 4 characterised in that the pharmaceutically active material is selected from one or more of antigens, antibodies or pharmaceutical substances.

6. The composition according to any of the claims 1 to 5 characterised in that the composition additionally comprises one or more of pharmaceutically acceptable excipients or adjuvants.

7. A process of preparing a composition according to any of the claims 1 to 6 characterised in that it includes the steps of:

a) mixing an effective amount of a pharmaceutically active material with the polytartrate polymer,

b) shaping the mixture by a tabletting equipment to form compressed tablets.

8. The process according to claim 7 characterised in that the pharmaceutically active material and the polytartrate polymer are mixed in a powdered form.

9. The process according to any of the claims 7 to 8 characterised in that the mixture is sieved and optionally additional tabletting excipients are added to the mixture.

10. The process according to any of the claims 7 to 9 characterised in that the compressed tablets are formed at a compression force between 15 and 65 kN/cm_2, preferably between 25 and 50 kN/cm^2.

11. Use of the composition according to any of the claims 1 to 6 for the manufacture of a product for the prophylaxis or treatment of diseases in humans or animals for parenteral administration.

Abstract

The invention provides a polytartrate composition for pulsatile release of a pharmaceutically active material that is in the form of a compressed tablet, a process for preparing such a composition and the use thereof.

Figure 1: In vitro release from PTA tablets containing 10 % Buserelin

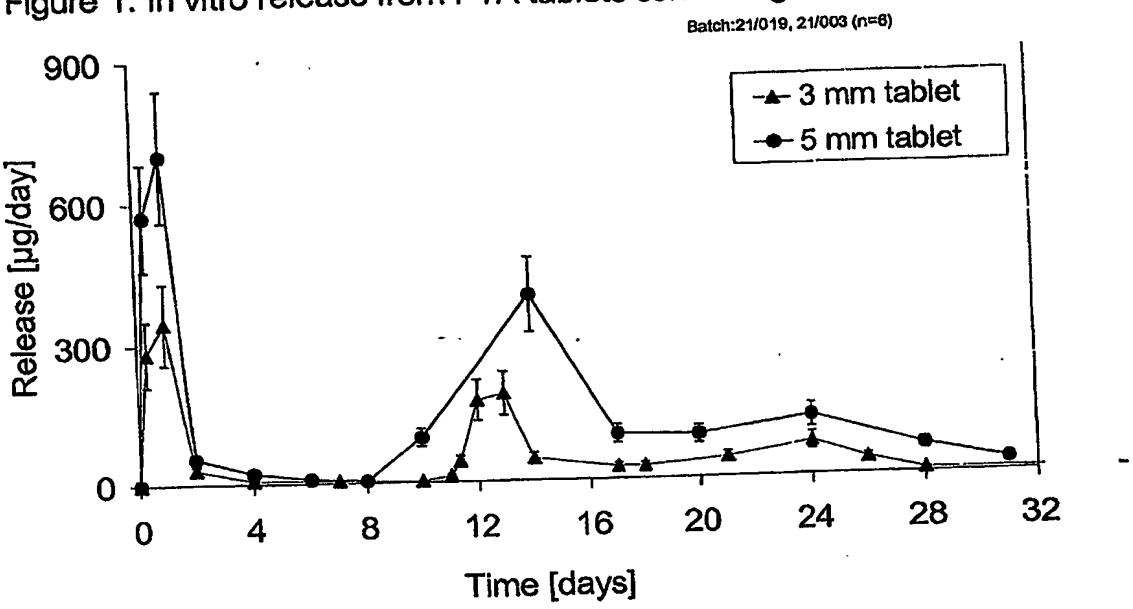

Figure 2: In vitro release from 3 mm PTA tablets: influence of drug load